

WHAT IS CLAIMED IS:

1. A method of creating hybrid proteins having a common biological activity comprising the steps of:
  - (a) creating a library comprising 32 or more nucleic acids encoding a plurality of hybrid protein members, wherein the members differ from a set of at least two parent proteins with corresponding amino acids, and
    - i. where the parent proteins are homologous proteins having greater than 60% amino acid similarity to each other and having at least one common biological activity,
    - ii. where a majority of the library members have a greater than 60% amino acid similarity to any of the parent proteins, and
    - iii. where the majority of differences between the library members and the parent proteins are confined to those corresponding amino acids that differ among the parent proteins;
  - (b) expressing protein from at least one library member to create at least one hybrid protein;
  - (c) selecting at least one protein having a common biological activity of the parent proteins.
2. The method of claim 1, wherein the parent proteins are enzymes.
3. The method of claim 1, wherein the parent proteins are isozymes.
4. The method of claim 1, wherein the parent proteins are polymerases.
5. The method of claim 1, wherein the parent proteins have greater than 80% amino acid similarity to each other and the majority of the library members have greater than 80% amino acid similarity to any of the wild-type proteins.
6. A library comprising nucleic acids encoding a plurality of hybrid protein members, wherein the members differ from a set of at least two parent proteins with corresponding amino acids, and
  - i. where the parent proteins are homologous proteins having greater than 60% amino acid similarity to each other and having at least one common biological activity,

ii. where a majority of the library members have a greater than 60% amino acid similarity to any of the parent proteins, and

iii. where the majority of differences between the library members and their parent proteins are confined to those corresponding amino acids that differ among the parent proteins.

7. The method of claim 6, wherein the parent proteins are enzymes.

8. The method of claim 6, wherein the parent proteins are isozymes.

9. The method of claim 6, wherein the parent proteins are polymerases.

10. The method of claim 6, wherein the parent proteins have greater than 80% amino acid similarity to each other and the majority of the library members have greater than 80% amino acid similarity to any of the parent proteins.

11. A synthetic hybrid protein comprising greater than 60% amino acid similarity to each member of a set of at least two parent proteins, where each parent protein in the set shares greater than 60% amino acid similarity and at least one common biological activity with each member of the set, and wherein the set comprises a subset of invariant amino acids that are identical among all members of the set, and wherein the hybrid protein:

(a) shares at least one biological activity with all members of the set;

(b) comprises at least 95% of the subset of invariant amino acids

(c) has a minimum of 5 amino acid residue differences from any member of the set; and

(d) contains at least 5 variable amino acid residues corresponding to alternating parent proteins.

12. The hybrid protein of claim 11, wherein the parent protein is an enzyme.

13. The hybrid protein of claim 11, wherein the parent protein is an isozyme.

14. The hybrid protein of claim 11, wherein the parent protein is a polymerase.

15. The hybrid protein of claim 11, wherein the synthetic protein comprises greater than 80% amino acid similarity to each member of the set and wherein each wild-type protein in the set shares greater than 80% amino acid similarity with each member of the set.

16. A hybrid protein of claim 11, wherein the set of parent proteins comprises the *Pyrococcus furiosus* family B DNA polymerase and *Pyrococcus* ssp. GB-D DNA Polymerase and the differences from any member of the set comprise at least 10 of the mutations selected from the group listed in Figure 8.